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## VARICELLA ZOSTER VIRUS MENINGITIS COMPLICATING SODIUM STIBOGLUCONATE TREATMENT FOR CUTANEOUS *LEISHMANIASIS*

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**Abstract.** Sodium stibogluconate (Pentostam®; GlaxoSmithKline) is a pentavalent antimonial compound used in the treatment of leishmaniasis, which has an association with reactivation of varicella zoster virus (VZV). We report the first known case of an immunocompetent adult who developed VZV aseptic meningitis and dermatomal herpes zoster during treatment with sodium stibogluconate.

### INTRODUCTION

Leishmaniasis (CL) is a significant health concern for the U.S. Armed Forces, with more than 700 cutaneous cases diagnosed in servicemen deployed in support of Operation Iraqi Freedom.<sup>1</sup> Treatment options available for patients infected with Old World cutaneous leishmaniasis range from observation for patients with mild disease to the administration of parenteral sodium stibogluconate for patients with more significant lesions. Sodium stibogluconate is known to result in several predictable side-effects including arthralgias/myalgias (58%), elevated pancreatic enzymes (97%), elevated liver-associated enzymes (67%), headache (22%), and hematologic suppression (44%).<sup>2,3</sup> Herpes zoster temporally associated with the administration of sodium stibogluconate has also been reported, perhaps secondary to transient lymphopenia.<sup>4</sup> In this report, we describe a patient who developed aseptic meningitis and herpes zoster secondary to varicella zoster virus (VZV).

### CASE REPORT

A 21-year-old Caucasian male Army soldier with relapsed cutaneous *Leishmania major* infection was treated at Walter Reed Army Medical Center (WRAMC), Washington, D.C., with a second course of intravenous sodium stibogluconate dosed at 20 mg kg<sup>-1</sup> day<sup>-1</sup>. His past medical history included chickenpox as a child, eczema, and atopy. On the 17th treatment day he noted onset of a headache, which increased in severity over the next day and was associated with retro-orbital pain, photophobia, neck stiffness, nausea, and vomiting. Upon evaluation in the emergency room, he had a temperature of 101.6°F, mild nuchal rigidity, a skin examination showing healing leishmaniasis sores and petechial appearing patches under the right axillary area as well as back. His neurologic examination was normal, including mental status. His baseline white blood cell count (WBC) prior to the initiation of sodium stibogluconate was 9,200/cmm with 31% lymphocytes. At the time of evaluation for his meningeal symptoms, his WBC count was 8,000 (11% lymphocytes) and his CD4 count was 403/cmm. A magnetic resonance imaging of the brain was normal. Cerebrospinal fluid (CSF) sampling

showed WBC 868 (82% lymphocytes), RBC 28, protein 97 (normal 12–60 mg/dL), and glucose 48 mg/dL (serum glucose was 82). Serum ELISA testing for HIV was negative. The next day, a clustered vesicular rash was evident in the right thoracic T1 dermatome, and direct fluorescent antibody testing of a scraping from a vesicle was positive for VZV. Cerebrospinal fluid VZV DNA PCR (MRL reference laboratory, Cypress, CA) was positive. Insufficient CSF remained for VZV antibody testing although serum VZV IgM was 0.36 (0–0.6 ISR) and IgG 3.30 (0–1.09 ISR). The patient was initially treated with intravenous acyclovir with marked improvement in his symptoms and completed a 7-day course of therapy with valacyclovir (Valtrex®). Sodium stibogluconate was discontinued after a total of 18 doses, and at a 2-month follow-up, he reported healing of his skin lesions and no sequelae after the VZV meningitis.

### DISCUSSION

To our knowledge, this case represents the first report of VZV meningitis as a potential complication of sodium stibogluconate use for the treatment of cutaneous leishmaniasis. Pentavalent antimonials, such as sodium stibogluconate, have previously been described in association with reactivation of dermatomal herpes zoster.<sup>4</sup> The etiology for the reactivation of VZV in patients receiving sodium stibogluconate is not known but may result from a transient lymphopenia and immunosuppression.<sup>4</sup> A prior study noted that an acute decline in CD4 cells (median decrease of 306/cmm) and total lymphocytes (median decrease 804/cmm) at Day 7 of treatment with sodium stibogluconate may be contributory.<sup>4</sup> In that study, reactivation of herpes zoster typically occurred near the completion of a 20-day treatment course, as in this case, or within the subsequent month. To date, including our original report of herpes zoster associated with sodium stibogluconate, we have observed a total of 12 cases [12 of 495 total patients (2.4%)].

The incidence of herpes zoster observed in our population is greater than published rates. Three recent studies have reported the incidence of herpes zoster. Insinga and others reported data from the Medstat MarketScan database, which contains more than 4 million U.S. citizens. The incidence was 1.2 cases per 1,000 person-years and 1.9 cases per 1,000 person-years for patients age 15 to 29 and 30 to 39, respectively, in their population.<sup>5</sup> A second study by Jumaan and others reported an incidence of 0.34 cases per 1,000 person-years for

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adults age 20–59 in 2002 for a Washington State HMO.<sup>6</sup> A third study reported the rates in the U.S. Armed Forces between 1998 and 2001.<sup>7</sup> In this study, the overall rate was 1.14 cases/1,000 person-years. The rates increased in every decade but even in adults greater than age 40 the overall rate was only 2.04 cases per 1,000 person-years. The rate observed in our population was approximately 24 cases per 1,000 person-years (95% Poisson CI 12.4 to 41.9 cases per 1,000 person-years), which was significantly greater than any other reported rate when compared by z-test ( $P < 0.001$ ) suggesting sodium stibogluconate usage is a risk factor for developing herpes zoster.

The current case is unique because the patient had VZV meningitis confirmed by PCR, in addition to the dermatomal manifestations reported previously in association with sodium stibogluconate use. The advent of more sensitive diagnostic tests has suggested a prior under-recognition of acute neurologic involvement in reactivation VZV, and reports indicate that VZV is often being identified as the cause of aseptic meningitis.<sup>8,9</sup> However, VZV DNA is known to be present in the CSF of patients with herpes zoster even in the absence of clinical meningitis, and a sampling of CSF in immunocompetent adults with herpes zoster but no other neurologic symptoms found CSF pleocytosis in 46% and 24% (10 of 42) had a positive CSF VZV PCR.<sup>10</sup> Although VZV may have been detectable by PCR in the CSF of the previously reported sodium stibogluconate-treated patients with herpes zoster, they did not have clinical symptoms of meningitis, and thus lumbar puncture was not performed. The clinical history and CSF findings in this case support VZV as the etiology of the patient's aseptic meningitis.

Sodium stibogluconate has been used for the treatment of leishmaniasis since the 1940s but is rarely prescribed by most medical professionals. In the United States, sodium stibogluconate is available only through an investigational new drug protocol from WRAMC and Brooke Army Medical Center, San Antonio, Texas (for military personnel), and from the Centers for Disease Control, Atlanta, Georgia (for civilians). With many U.S. military members and civilian contractors deployed to leishmaniasis-endemic areas of the world, and with hundreds of cases identified in the past year, the use of sodium stibogluconate among American medical providers has increased. Sodium stibogluconate, while efficacious for leishmaniasis, is associated with a variety of toxicities, and aseptic meningitis secondary to VZV can now be added to that list.

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